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NUTRITION REVIEWS

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NUTRITION REVIEWS

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APPRAISAL OF THE NUTRITIONAL STATE OF CHILDREN IN PROGRAMS OF RELIEF FEEDING

The selection of those children in a population who are in greatest need of supplemental feeding has always been difficult. The modern knowledge of nutrition has complicated rather than simplified this undertaking for it is now recognized that the nutritional state of children cannot be properly evaluated without a comprehensive series of observations involving biochemical and other technical procedures as well as clinical examinations. The examination of all children in a community for the purpose of selecting a limited number for whom relief feeding can be provided is not justified by the results obtainable from procedures which can be applied on such a large scale. For small scale operations reliance must usually be placed upon local physicians or social workers to decide which children are in greatest need, even though experience has shown that this method fails to discover some of the most needy while referring many children in far better circumstances. When feeding programs are to be national in scope and can provide for large classes or sections of the child population, it is necessary to determine the best use of the foods available or the amounts and kinds of food required. Where choice must be made between giving all children too little or too few children enough, or as to the age groups to be fed and the areas to be included, reliable data as to the incidence and severity of the various types of malnutrition are essential. All large scale relief feeding programs should therefore be preceded by a nutritional survey, and follow-up surveys should be repeated from time to time to keep abreast of changing conditions. Such investigations may be limited to study of official reports and interviews with public health officials, practicing physicians, and hospital authorities, but special studies are required to assure the most efficient use of the foods available. It is now generally recognized that intensive study of the diets and physical condition of small groups of children is preferable to less comprehensive studies of larger numbers, provided the groups are carefully chosen to be truly representative of the population as a whole.

Surveys designed to guide relief programs of national scope could in many instances be carried out at medical centers by persons residing in the countries concerned. In some countries, however, sparsity of population and lack of sufficiently well developed medical centers would make this impossible. In any case the need for uniformity of procedure would require a long period of preparation and continual close supervision of the investigations while in progress. The survey made by the American Red Cross in unoccupied France during the late fall of 1942 was carried out by the staffs of three medical schools and one research institute, and in Monaco by the state hospital. The chief difficulties encountered were, that only children in urban communities could be studied, and that much time was required for explanation of the purposes and methods of examination, and for training the operating staffs in uniform technical procedures.

On the basis of experience in France, the conclusion seems inescapable that an organization setting out to distribute large quantities of food in any country sufficiently demoralized to require relief feeding, should send to that country in advance of food shipments a complete mobile survey unit. This should include a well trained staff of adequate size and composition to make all important examinations without local

assistance, full equipment in portable form including record forms and all materials required for clinical, laboratory, and x-ray investigations, and adequate transportation facilities. An attempt should always be made to use capable native talent and to encourage participation by cooperative local organizations as far as possible without sacrificing reliability in the data obtained. This should be done in order to assure the maximum of local support and the most satisfactory and enduring influence upon the medical thought and practice of the community. In some instances reliance upon local assistance should probably not go beyond that of securing accommodations and the presence of suitably selected children at examinations. In other instances, much of the routine of clinical and laboratory work could undoubtedly be done by local assistants under close supervision.

As the problem of evaluation of nutritional status is primarily medical and concerns children, the program should be planned and carried out under the direction of a pediatrician who has special interest both in nutrition and in public health. These special interests should have been developed to the point of making him conversant with the laboratory methods accepted as useful adjuncts to nutritional assessment and with the statistical methods involved in reliable sampling and the correct interpretation of data obtained from group studies. He must have a sympathetic understanding of the problems, activities, and methods of those who administer relief programs as well as of public health officials. It is important, also, that the administrator of the relief activities understands the purpose of the medical survey and is prepared to give the medical director full cooperation.

The medical director should have a medical assistant, chosen with the intent of having him complement his chief in those fields of technical knowledge where support is most needed. For example, if the chief is primarily a clinician and interested in the public health aspects of nutrition, his assistant might well be chosen because of his technical knowledge of the laboratory aspects of nutritional assessment. There should be a staff of carefully chosen assistants in specialized fields. At a minimum, this would consist of one public health nurse, one nutritionist, one or two laboratory technicians, and a roentgenologic technician. The public health nurse would be responsible for the children during the examinations and would assist at certain procedures such as weighing, measuring, and taking blood samples. She would arrange the clinic schedules and make the necessary contacts with the local nurses, social workers, or volunteers who would bring the children from the schools. In the absence of a record secretary, she would make certain that all data were filed and the record forms completed. A record secretary with some knowledge of statistics would be a valuable addition to this staff. The nutritionist would be required primarily to take diet histories to determine the actual food consumption of the children of different ages, but she could also be of great assistance in gathering and analyzing general information pertaining to available food supplies and rations. A man responsible for the transportation and setting up of the equipment would be desirable but this work might be handled by the technicians or by someone employed locally. Some if not all of these should speak the language of the country but some persons could undoubtedly be found in the country concerned who would be qualified to serve as assistants to staff members, both as interpreters and in the actual carrying out of the routine. A truck would be required for the transportation of the portable x-ray unit, laboratory equipment, and supplies. One or two station wagons would be desirable for the transportation of the staff.

A member of the survey staff should visit each community in advance of the arrival of

the regular examining team. The medical director himself might leave the work at one center, when well under way, in the hands of his assistant and visit the next center to carry out the organizational work. Under a more elaborate program there might be an additional person who would act as business manager and spend most of his time preparing the ground in advance of the traveling unit. It would then be necessary only to explain the program to various local groups whose cooperation would be desired, to arrange for the selection of a representative group of children after studying local dietary and economic conditions, and to find suitable quarters and a few persons who might assist at the examinations. All need for training local personnel and reconciling differences of opinion in regard to the examinations themselves would thus be eliminated.

The examination form should be in code form and should provide for the recording of various kinds of data in a precise and standard manner. This would reduce to a minimum the work involved in transferring the data to punch cards and would allow for rapid sorting, counting, and tabulation of results. The special features of the local situation would have to be taken into account in planning the actual examination form to be used in any particular country. However, if a master form were worked out in advance by the relief agency, its revision and translation for use in a specific situation could be easily accomplished. Lists of the equipment and supplies that would be needed should be made complete in every detail, and no reliance should be placed on finding any of these in the country where the study is to be made.

The selection of the children to be studied and the nature and size of the groups to be sought cannot be discussed at this time. In principle only a few categories would be established and the number in each category at each center would be small. Examinations should be made at several centers, both urban and rural, as local food situations often differ considerably. The groups of children selected should include three or four age groupings of both sexes separately, but no one group should include an age range of more than one year.

The cost of a survey carried out along these general lines may at first appear to be excessive, but in comparison with the amount likely to be spent on the food and its distribution, it would not be so. The most intelligent and scientific use of funds contributed to meet the needs of an undernourished population should be guaranteed as far as possible, and considerable expense would be necessary and justifiable in order to assure this end.

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NUTRITIONAL DEFICIENCIES IN THE UNITED STATES

The Committee on Diagnosis and Pathology of Nutritional Deficiencies of the Food and Nutrition Board of the National Research Council has published an extensive report on "Inadequate Diets and Nutritional Deficiencies in the United States; their Prevalence and Significance" (*Bull. National Research Council no.* **109**, *Nov.* (*1943*)). It is of interest to note how this Committee has planned its survey of available evidence. Like an earlier publication on the prevalence of malnutrition by Jolliffe, McLester, and Sherman (*J. Am. Med. Assn.* **118**, *944* (*1942*)) the present Committee of which H. D. Kruse is Chairman, has divided the report into two main sections, one on dietary surveys and the other on the medical evaluation of nutritional states.

The report begins by pointing out that every dietary survey in the past decade has shown that the foods eaten by the people in the United States are such that they do not supply the dietary essentials in amounts which are considered desirable by most nutritionists. The standards used by the Committee are the recommended allowances developed by the Food and Nutrition Board. These standards are admittedly liberal but it should be remembered that accumulating evidence indicates the wisdom of high standards. If people are to secure the maximum benefit from advances in nutrition they probably should set their goal high. Few persons would disagree with the view that dietary improvement is desirable when 26 per cent of a group of people are found to be ingesting less than 50 per cent of the recommended levels for riboflavin, 13 per cent less than half the recommended allowances for thiamin and calcium, 5 per cent less than half the allowances for calories and for vitamin A, and 4 per cent less than half the recommended intakes of ascorbic acid. Yet these results have been reported in a study of 225 private patients in the upper income brackets examined in Philadelphia in 1940 by Kelly and Sheppard. In this group were nine physicians whose diets were no better than those of the patients. The results of other studies on people in lower income groups, as might be expected, show an even greater deficiency when compared with recommended dietary allowances. As a matter of fact, when records of the individual foods consumed by any group of people are examined one wonders how the human race ever has managed to get along as well as it has.

There were 22 extensive dietary surveys made in many different sections of the country in the years 1938 to 1940 inclusive, and several more during the next three years. It can only be concluded from this evidence that a considerable proportion of our population is not devoting as much attention as it should to the foods it eats. An illuminating series of tables prepared by the Committee shows the percentages of persons with intakes of the respective dietary essentials at less than recommended levels, at less than 75 per cent of recommended levels, at less than 50 per cent, and at less than 25 per cent. Who would gainsay the assertion that more vitamin C is needed if a survey of 56 white children 15 years old and over shows that 52 per cent of these persons are receiving less than one fourth of the recommended level of ascorbic acid, and 49 per cent of 39 Negro children in the same age group likewise are receiving less than one fourth of the recommended allowances for this dietary essential? Yet these are the results obtained by D. F. Milam in North Carolina and reported to the Committee, and these records were made during the summer months.

There is great interest of course in the section devoted to deficiency states as revealed by medical examination. This section of the report is principally defensive in tone since it emphasizes the use of new methods, the validity and interpretation of which are not yet generally accepted. The report does not help much in bridging a gap previously noted in this journal (*Nutrition Reviews* **1,** *33 (1942)*) between the widespread prevalence of inadequate diets and the relatively small proportion of clinically detectable instances of nutritional deficiency. Perhaps this criticism is a bit unjust because a review cannot be expected to provide more evidence than is obtainable in the scientific literature. However, readers can expect to find a discussion of all important evidence on a subject, a critical evaluation of this evidence, with conclusions and suggestions for further investigation. The Committee has assumed a difficult assignment, and the question arises, how has this task been handled?

In the introductory portion of the medical section of the review attention is directed to the hypothesis of Kruse that most deficiency states, like many other diseases, should be considered in terms of mild acute,

mild chronic, and severe chronic cases. The classic description of deficiency disease has been applied, in the past, to what might be called the severe acute case. As a result of his experience, particularly with the use of the biomicroscope, Kruse believes that physicians should look for various morphologic changes which he considers are characteristic of deficiency states less severe and more chronic than the florid deficiencies. His hypothesis is not only interesting but it is one worthy of exhaustive study. On the other hand it does not seem that the evidence available to date justifies some of the statements provided in the present report. With regard to these minute morphologic changes the Committee has written, "So common, so prevalent, so frequently seen are some of these changes, especially their slighter degrees, that they have been regarded as usual or normal. But their specific location, distinctive and characteristic nature, their reversibility, all attest to their pathological identity as deficiency states." Though stated with enthusiasm, most clinical investigators believe that there simply has not been enough time nor sufficient confirmatory evidence to justify so positive a declaration in the report of the Committee. No mention is made of the fact that the sclera, cornea, gums, and tongue are tissues particularly susceptible to many types of minor trauma and which consequently vary slightly in their morphologic pattern. The Committee does not seriously consider that the lesions mentioned are not specific and may occur even when no nutritional deficiency is present. Would it not be better frankly to admit that we do not have at hand tried and true methods for demonstrating the effect of mildly inadequate diets on the human being, although some of the newer methods of evaluation of the nutritive status have much promise?

The main body of the medical section of this report includes a brief discussion of the records of severe acute deficiencies as revealed by official mortality and hospital admission rates. The data from these sources show a small incidence of acute deficiency conditions in the United States. Doubtless the criticism of the Committee of these records is justified, for many cases of acute deficiencies must go unrecognized or unrecorded because of the nature of the record keeping and the fact that human beings are frequently subjected to a combination of diseases at the same time. There is a review of the data provided by studies of hemoglobin concentration of the blood, the amount of ascorbic acid in the plasma, of urinary riboflavin and of serum protein concentration. The report does not present a critical appraisal of the interpretation of these data, particularly urinary excretion tests for riboflavin. The point is well made that if concentrations of ascorbic acid in the blood plasma below 0.6 mg. in each 100 ml. are an indication of deficiency, then a considerable number of people need more vitamin C. All surveys have shown that there is a considerable number of people who have low hemoglobin values. This fact is of interest because dietary surveys indicate that on the whole the iron intake is satisfactory. There is evidence also that the recommended dietary allowances of iron are liberal. The fact that anemia does occur needs emphasis, for it indicates perhaps that more factors than we know of are concerned with the maintenance of good nutritive conditions with respect to hemoglobin formation. As always in applying the results of experimental studies to human feeding problems there is need for maintaining a broad and conservative outlook, through realization that we do not yet know all the facts.

The section on purely medical assessment of the nutritional status is devoted to a discussion of objective signs such as the polyneuropathy of thiamin deficiency; cheilosis, angular stomatitis, and other changes associated with riboflavin deficiency; xerosis conjunctivae of vitamin A deficiency; signs of rickets; the lingual manifestations of ni-

acin deficiency, and the gingival lesions of ascorbic acid deficiency. Most ophthalmologists as yet do not agree with the contention of Kruse that the condition which he has termed xerosis conjunctivae is associated with vitamin A deficiency. Yet the Committee asserts that all the evidence is in agreement that deficiency states are common among the people of the United States.

The Committee has devoted little attention to the so-called subjective signs of deficiency conditions. These are sometimes included under the heading "vague symptoms," but though difficult or impossible to describe and measure they are real and important, and may be caused by nutritional inadequacy. The influence of good nutritional status on such things as irritability, equanimity of behavior and learning ability are probably just as important as the minor morphologic changes which have been studied with the aid of the biomicroscope. The report makes little mention of the considerably large majority of clinical and laboratory experience which is not in harmony with the Committee's statement and general thesis that "deficiency states are rife throughout the nation."

The final section of the report is concerned with the significance of deficiency states and optimum nutrition. The Committee refers to the effects of diet on growth and development, childbearing, well-being and efficiency, dental caries, and on susceptibility and resistance to infections. The report will be of distinct interest and value to students of nutrition. The bibliography contains 189 references, chiefly to publications since 1933, and many of the tables are based upon recalculations that facilitate comparison of data. The nutrition worker of today is a little in the position of a stonemason chipping away at the base of a tall building, trying to learn about its structure, wondering about its functions, eagerly groping for some knowledge of the architect's plans. No doubt Nutrition Reviews twenty five years from now will look back on some of the assertions of today as examples of prophetic vision, but the urgent need of the time is more and still more research—to supply the data and facts that simply are not available today.

PHARMACODYNAMIC ACTIONS OF VITAMINS

Vitamins might be expected to display at least some physiologic activities apart from their function as trace catalysts in metabolism. Although vitamins appear to be relatively lacking in pharmacodynamic properties (*Nutrition Reviews* **1**, *233 (1943)*), the intensive study of vitamins is actually more liable to disclose secondary physiologic functions for these substances than for other classes of organic substances. The reports of niacin in the treatment of angina pectoris, and thiamin for relief of pain following dental extraction (*Ibid.* **1**, *43, 157 (1943)*) are instances of possible vitamins acting as drugs. Recently there have been reports of ascorbic acid acting as a diuretic, and vitamin D as an agent affecting capillary permeability.

In reports of this type, doses of vitamins are employed which are far in excess of amounts required to produce changes in nutritional status. In general, these studies do not claim that the therapeutic action of the vitamin is in any way concerned with a nutritional deficiency state in the patient. Nevertheless such studies, although more properly within the pharmacologist's domain, must receive the attention of the nutritionist because of the tendency for some to interpret the results solely from the nutritional standpoint.

The action of vitamin C as a diuretic has origin in the animal experiments of Fliederbaum and Tislowitz (*Ztschr. f. d. ges.*

exp. Med. **97**, *121* (*1936*)) in which injection of this vitamin caused a diuresis associated with an increase in the blood colloid osmotic pressure. It was noted that in contradistinction to the effect of acid-producing salts when they potentiate the mercurial diuretics, the blood plasma carbon dioxide combining power subsequent to injection of ascorbic acid was uniformly increased (Tislowitz, *Compt. rend. soc. Biol.* **121**, *916* (*1936*)). It was assumed in these studies that the diuretic action was produced by the "polyphasic effect of ascorbic acid on the colloid osmotic pressure of the blood."

Shaffer (*J. Am. Med. Assn.* **124**, *700* (*1944*)) reports observations in patients with peripheral edema. In the first experiment there were 5 men and 5 women 20 to 60 years of age in whom the edema was attributed to cardiac decompensation. Each had remained in bed and received the standard hospital diet for three days prior to the use of ascorbic acid and during this period were in a relatively stable fluid balance. All were receiving a maintenance dose of digitalis, and their fluid intake was regulated at 1500 ml. in twenty-four hours. When these patients received daily 500 mg. of methylglucamine ascorbate by mouth in divided doses, there was an increased urine excretion of 250 to 1000 ml. in seventy-two hours. In contrast, another 10 patients who received the same amount of ascorbic acid or even as much as 3 g. by vein, showed no increase in the quantity of urine excreted. Finally 20 patients were given 500 mg. of ascorbic acid in addition to 2 ml. of mercupurin, a mercurial diuretic. The diuresis which followed in 15 of these patients was increased from one-half to two and one-half times that produced by mercupurin alone. The actual increase was from 500 ml. to 2000 ml. in twenty-four hours. A smaller output was noted in the other 5 patients.

No statement was given concerning the status of the patients with regard to ascorbic acid unsaturation, although there may be reason to expect that patients suffering from such a chronic ailment would be partially deficient in vitamin C. However, no claim was made that the therapeutic action might be a nutritional effect, nor is there adequate basis for such a contention.

The second report concerns a pharmacodynamic action of vitamin D. On the basis of a single experiment it was claimed by Tislowitz and Kurowski (*Biochem. Z.* **291**, *73* (*1937*)) that large doses of vitamin D produce an increase in the plasma volume of circulating blood together with a decreased red cell volume. In a more recent communication Silver, Steck, and Reed (*J. Lab. Clin. Med.* **29**, *48* (*1944*)) present further observations on this subject.

The method used for determining changes in capillary permeability was the disappearance rate of the dye T-1824 from the blood stream of the dog. Dosages of 45,000 to 110,000 I.U. per kilogram administered in twenty-four to forty-eight hours were followed by a greatly increased disappearance rate of the dye, and both plasma volumes and hematocrit values were much increased. Following the injection of histamine in normal dogs, the hematocrit value rose sharply, which suggested a loss of fluid from the blood. After the administration of vitamin D, the changes in the blood following histamine were less pronounced. The authors compared the increase of dye concentration in lymph with the decrease of dye concentration in serum and found a good linear correlation, which tends to confirm the validity of their observations. Lower daily doses (10,000 to 15,000 I.U. per kilogram per day) or as much as 20,000 I.U. per day for as long as seven days, were not associated with significant changes. Such results divorce the vitamin D action from the realm of nutritional significance. Interpretation of the mode of action of the larger doses of vitamin D can be only a matter of speculation.

EFFECT OF NUTRITION ON PHAGOCYTOSIS

Nutritional deficiencies apparently cause decreased resistance to certain types of infection (*Nutrition Reviews* **1**, *66*, *298* (*1942–43*)). Many investigators have attempted to explain this phenomenon but their results have been disappointing. Except in protein deficiencies (*Nutrition Reviews* **1**, *186* (*1943*)), production of antibodies by deficient animals does not seem to be impaired (Clausen, *Physiol. Rev.* **14**, *309* (*1934*)). Cottingham and Mills (*J. Immunol.* **47**, *493*, *503* (*1943*)) therefore, decided to determine whether nutritional deficiency interfered with the phagocytic activity of white blood cells and thus lowered resistance. They have accumulated evidence which indicates that deficiencies of thiamin, riboflavin, pyridoxine, pantothenic acid, choline, ascorbic acid, and protein reduce phagocytic activity. Combined vitamin A and D deficiency produces the same effect, but inositol and p-aminobenzoic acid do not seem to influence phagocytosis.

Cottingham and Mills made both *in vitro* and *in vivo* observations. Young white male mice were used for the former experiments and were fed a purified diet composed of sucrose, casein, corn oil, salts, and vitamin supplements. The vitamins were added to the diet directly in the following amounts per kilo of ration: haliver oil 1.2 ml., riboflavin 4 mg., pyridoxine 4 mg., calcium pantothenate 6 mg., niacin 100 mg., inositol 1 g., and p-aminobenzoic acid 0.3 g. The thiamin and choline contents of the ration were varied from 0.5 to 8.0 mg. and 0.1 to 5.0 g. per kilo respectively. One group of animals was kept in an air-conditioned room at 68°F. and another in an air-conditioned room at 90° to 91°F. with 60 to 70 per cent relative humidity. The hot moist environment was used because of its possible effect in increasing vitamin requirements (*Nutrition Reviews* **1**, *426* (*1943*); **2**, *127* (*1944*)). After three weeks on the experimental diet and of exposure to the hot and cold environments, each mouse was injected intraperitoneally with 0.5 ml. of a twenty-four hour culture of a virulent type I pneumococcus diluted 1 to 100 in broth. Control observations had shown that the outpouring of neutrophiles and monocytes into the peritoneal cavity under these circumstances reached its height at the end of four hours. Consequently, films of the peritoneal exudate were prepared four hours after the intraperitoneal inoculation. The percentage of neutrophiles and monocytes was determined and count was made of the cells which had ingested pneumococci. The authors state that the films "were highly unsatisfactory and variable as a basis for cell and phagocytosis counts," but the results did assume a general pattern. Phagocytic activity of both types of cells was much less at the lower levels of thiamin intake (0.5 and 1.0 mg. per kilo of ration) than at the higher levels (4.0 and 8.0 mg.). Furthermore, at these latter levels, the phagocytic activity was greater than when only enough of the vitamin was provided to produce optimum growth. From the data provided, no clear difference in phagocytosis was shown between the hot-room and cold-room animals. Results with choline were much less distinct.

Because the technic of studying films of the peritoneal exudate was unsatisfactory, Cottingham and Mills used an *in vitro* method for the remainder of their experiments. To 0.5 ml. heparinized blood, obtained by cardiac puncture from rats fed a similar type of diet and kept under the same environmental conditions, was added 0.5 ml. of salt solution and 0.2 ml. of a standard bacterial suspension of Micrococcus candidus. After the mixture had been placed in a water bath at 38°C., and shaken for four minutes to prevent clumping of the leucocytes, films were made and stained with Wright's stain. One hour later, additional films were prepared and examined to determine how much digestion of the phagocytized bacteria had

occurred. The number of ingested bacteria found in forty or fifty unruptured and unclumped neutrophiles was counted. The experimental ration was modified so that graded reductions in one vitamin at a time were made and fed to separate groups of rats. From four to seven weeks on the diets were required to bring out the growth-retarding effects of the deficient diets. In every series of experiments, deficiency of thiamin, riboflavin, pyridoxine, pantothenic acid, or choline sufficient to retard growth also caused a significant reduction in the phagocytic activity of the white blood cells. Usually intracellular digestion of the bacteria was also retarded. Both effects were most noticeable in animals kept on a riboflavin or pyridoxine deficient diet for seven weeks. Preliminary tests indicated that lack of both vitamins A and D in the same animal produced a similar result. Inositol and p-aminobenzoic acid did not influence phagocytic activity. In all instances, phagocytic activity was equally good in animals kept under the two different environmental conditions so long as optimal supplies of the nutrients were available. Greatest phagocytic activity, furthermore, seemed to occur at levels of vitamin intake greater than those needed for good growth. It is also interesting that when a vitamin was entirely removed and the condition of the animal became critical, phagocytic activity of its leucocytes often became stimulated.

Guinea pigs were used as a source of blood from vitamin C deficient animals. Young pigs were fed a diet of wheat bran, rolled oats, and dried skimmed milk. Haliver oil was given as a supplement and control animals were given leafy vegetables. Tests of phagocytic activity were made after three weeks. Observations were difficult because the leucocytes tended to fragment and clump. Even so, there was a marked reduction in the phagocytic activity of the blood from deficient pigs. This result is different from that obtained on human subjects deficient in vitamins A and C (Feller, Roberts, Ralli, and Francis, *J. Clin. Invest.* **21**, *121 (1942)*).

Study was also made of the effect of varying the protein in the diet at graded levels from 6 to 36 per cent. Weanling white male rats were used. Best phagocytosis and best growth were obtained in the cold-room rats when 18 per cent of the diet was protein (casein). Strangely, there seemed to be slight impairment of phagocytic activity as the protein intake was increased above this level. In the hot-room, on the other hand, both growth and phagocytic activity continued to improve with increased protein intake, even up to the 36 per cent level.

Under the conditions of these experiments, therefore, specific deficiency of certain of the vitamins and of protein apparently led to decreased phagocytic activity of leucocytes. If the observations can be confirmed, they will constitute an important contribution to our knowledge of the reason for decreased resistance to bacterial infections shown by deficient animals. Attention, however, has already been directed to contradictory results obtained by Feller and associates on human subjects deficient in vitamins A and C. The correlation of phagocytic activity with protein intake of the animals appears so striking that the effects of the vitamin deficiencies may be dependent on this factor, either through functional disturbance of protein metabolism or more simply by a possibly decreased protein intake coincident with the vitamin deficiency. Cottingham and Mills unfortunately give no data concerning the food intake of their animals. Furthermore, the data are presented in such a way that it is not possible to correctly evaluate the statistical significance of the results. The latter seems desirable since in most instances only forty cells were counted per smear, while in the experience of many workers in this field, counts of less than 200 cells cannot be relied upon to give a representative picture of the smear.

The danger of drawing conclusions from such data without statistical treatment is

strikingly demonstrated in the report that a direct relationship existed between the complement activity of serum and its ascorbic acid level, while careful repetition of the experiments by Kodicek and Traub (*Biochem. J.* **37**, *456 (1943)*) with statistical evaluation of the data failed to reveal any significant differences.

EXCRETION FORM OF NICOTINIC ACID

In the thiochrome method for the determination of thiamin in urine, Najjar and Wood (*Proc. Soc. Exp. Biol. Med.* **44**, *386 (1940)*) recognized a complication in the nature of an unknown substance which, like thiochrome, fluoresced in alkaline solution and was extracted by isobutanol. The fluorescent substance was later believed by Najjar and Holt (*Science* **93**, *20 (1941)*) to be a nicotinic acid derivative, and was designated by them F_2. This fluorescent substance had been found essentially absent in the urine of pellagrins or dogs with black-tongue, and this fact has been suggested as a basis for the detection of nicotinic acid deficiency.

Huff and Perlzweig (*Science* **97**, *538 (1943)*) recorded a marked chemical and biologic similarity of the previously announced F_2 and N′-methyl nicotinamide, and recently presented proof (*J. Biol. Chem.* **150**, *395 (1943)*) for the identity of these two substances. The proof consisted in the concentration of F_2 from urine and preparation of the picrate salt, which was identical with the picrate produced from N-methyl chloronicotinamide. The picric acid was presumed simply to displace chloride from the chloro derivative. Najjar and White (*Science* **99**, *284 (1944)*) do not consider the latter evidence adequate to prove the identity of F_2 and N′-methyl nicotinamide, nor that the F_2 precursor is the same as the chloro derivative. The latter workers confirmed the findings of Huff and Perlzweig but believe it possible that picric acid does more than simply replace the chloride group. They quote the work of Coulson and Ellinger (*Biochem. J.* **37**, xvii (*Proceedings*) (*1943*)) who showed that although the picrates of F_2 prepared from urine and N-methyl chloronicotinamide were identical, the aurate salts were different. Najjar and White, from a study of the chemistry of such derivatives and the isolation of F_2 itself, believe that F_2 is actually N-methyl nicotinamide alpha-carbinol. The highly fluorescent derivative is believed to be a butyl ether of this substance. The exact precursor of F_2 remains in doubt, although it seems certain that it is a derivative of N′-methyl nicotinamide.

Whether or not F_2 is the carbinol derivative or N′-methyl nicotinamide itself, it seems certain that the values obtained by earlier methods for "trigonelline" must have included this substance. Huff and Perlzweig indicate that at least in man and the rat, the N′-methyl derivative is the chief excretion product after the ingestion of either nicotinic acid or nicotinamide. The same authors (*J. Biol. Chem.* **150**, *483 (1943)*) have also pursued their findings to the practical end of developing a simple quantitative method for the N′-methyl derivative in urine as a possible basis for the detection of nicotinic acid deficiency. In this analytic method, the adsorption and elution of the F_2 precursor is eliminated, the fluorescence being developed directly in the diluted urine. In order to account for other urinary pigments, a blank is prepared after elimination of the N′-methyl derivative by the use of Lloyd's reagent. The analytic results were found to compare well with the more laborious permutit adsorption method. Unlike previous attempts to use "trigonelline" in the urine as a measure of nicotinic acid deficiency, the present method would not necessitate the restriction of trigonelline containing foods

such as coffee and legumes, since trigonelline does not affect the fluorescence method.

Since methylation of nicotinic acid is required before excretion of the N′-methyl form, the rate of methylation or the available "methyl" supply might also be a governing factor in the amount of derivative excreted. This may complicate the use of the excretion test as a measure of nicotinic acid deficiency. In this connection, Handler and Dann (*J. Biol. Chem.* **146**, *357* (*1942*)) have shown that the feeding of large amounts of nicotinamide to rats decreased their growth, probably by depleting their supply of available methyl groups, since methionine restored the growth.

Perlzweig, Bernheim, and Bernheim (*J. Biol. Chem.* **150**, *401* (*1943*)) were able to demonstrate the formation of F_2 from nicotinamide by rat liver *in vitro*. In these experiments methionine or choline were found to increase the rate of methylation, although irregularly. It is of interest that the liver is able to methylate nicotinamide but not the free nicotinic acid. Since nearly identical amounts of the N′-methyl derivative are excreted whether the amide or free acid is fed, it is evident that other tissues also participate in this phase of nicotinic acid metabolism.

Another irregularity that might be encountered in the excretion of the N′-methyl derivative was referred to by Perlzweig *et al.*, namely that individual rats on the same diet may vary widely in their excretion of methylated nicotinic acid. Two rats showing such extremes excreted 355 and 1030 micrograms of F_2 in twenty-four hours. The livers of these rats produced 17 and 32 micrograms of F_2 per gram of liver respectively, indicating that the variability in excretion was a function of the liver ability to methylate nicotinamide. This difference was not materially changed by addition of methionine.

It is difficult to predict to what extent such factors will affect the development of a laboratory diagnosis of nicotinic acid deficiency, but it is certain that this newer knowledge of nicotinic acid metabolism will be helpful in further progress.

RIBOFLAVIN DEFICIENCY IN THE MONKEY

As part of a well organized plan to study nutrition in the rhesus monkey, Waisman has produced what appears to be a pure riboflavin deficiency (*Proc. Soc. Exp. Biol. Med.* **55**, *69* (*1944*)), the manifestations of which were growth failure, a freckled dermatitis, incoordination of the limbs, and anemia. The latter is particularly interesting because the relationship of riboflavin to erythropoiesis and hemoglobin synthesis has not been clearly defined.

Waisman kept his animals in individual cages and fed them a highly purified diet consisting of sucrose 73, purified casein 18, salts 4, corn oil 3, and cod liver oil 2. The ration was supplemented daily with 1 mg. thiamin, 5 mg. niacin, 1 mg. pyridoxine hydrochloride, 3 mg. calcium pantothenate, 50 mg. choline chloride, 100 mg. para-aminobenzoic acid, 100 mg. i-inositol, 25 mg. ascorbic acid, and a 5 per cent level of a "folic acid" concentrate. Demonstration had already been made that the same diet + 1 mg. of riboflavin daily permitted rhesus monkeys to grow well and to remain in excellent health for at least fourteen months (Waisman and Elvehjem, *J. Nutrition* **26**, *361* (*1943*)). Under these experimental conditions, therefore, riboflavin was the only known essential nutrient lacking. The maximum riboflavin furnished daily by the "folic acid" concentrate was 10 micrograms.

Growth failure occurred after the animals had been on the deficient diet for six to eight weeks, although monkeys that had previously been fed diets containing liver

showed no signs of deficiency until after longer periods of time. Anorexia did not develop even after deficiency manifestations were advanced. In most of the monkeys, the first visible sign of deficiency was a freckled type of dermatitis which appeared first on the face and in the groin. The initial small, red, dry spots became increasingly prominent and enlarged until they appeared as dark scabs. Other areas of the body, particularly the arms and legs, became encrusted in the more severe cases. By the end of two or three months, an incoordination of the limbs was observed and the grasping reflex became faulty. Erythrocyte and hemoglobin values fell to anemic levels usually shortly after the appearance of the dermatitis. Low levels for the different animals were reached from fifty-nine to one hundred eight days after onset of the experiment. Hematologic data are given for only 6 animals; in these the hemoglobin varied from 4 to 9.7 g. and the red blood cell count from 1.7 to 3.02 million cells. White blood cell counts were also slightly below normal. The addition of biotin to the deficient ration either as a concentrate or in crystalline form neither influenced the development of the deficiency manifestations nor corrected them once they had appeared.

Administration of 50 micrograms of riboflavin per day to the deficient animals brought about remission of the milder and earlier cases of dermatitis within two or three weeks. When the deficiency was more advanced, 50 micrograms of riboflavin per day for thirty or more days were inadequate to give improvement. With larger doses (100 to 500 micrograms per day), however, there was remission of all the observed signs after ten to fourteen days. When the riboflavin was again withdrawn, the manifestations reappeared. The deficiency was produced several times in individual monkeys and each time responded to riboflavin administration.

The development of an anemia which was apparently corrected by riboflavin therapy is of particular interest since it provides a clear demonstration that the vitamin in some animals is important for normal erythropoiesis. In rats, anemia does not seem to be a consistent accompaniment of riboflavin deficiency. Sebrell and Onstott (*Pub. Health Reports* **53**, *83* (*1938*)) observed that an anemia was often present in dogs with ariboflavinosis, but that it did not respond to riboflavin feeding. On the other hand, György, Robscheit-Robbins, and Whipple (*Am. J. Physiol.* **122**, *154* (*1938*)) found that riboflavin increases the rate of hemoglobin production by the anemic dog. Patek, Post, and Victor (*Am. J. Physiol.* **133**, *47* (*1941*)) observed the development of an anemia in several riboflavin deficient pigs, but were of the opinion that the change resulted from lack of other food factors. In human subjects with supposed ariboflavinosis (cheilosis, magenta tongue, and corneal vascularization) and a coexisting hypochromic anemia, the anemia responded characteristically to iron therapy even though riboflavin administration was withheld (Moore, Minnich, Vilter, and Spies, *J. Am. Med. Assn.* **121**, *245* (*1943*)). Young men fed a diet restricted in riboflavin (0.31 mg. per 1000 calories) for eighty-four days showed no tendency to develop an anemia (Keys and associates, *J. Nutrition* **27**, *165* (*1944*)). It is apparent, therefore, that no clear proof exists that riboflavin is important to red blood cell formation and hemoglobin synthesis. For this reason, it is particularly regrettable that the hematologic data furnished by Waisman are so scanty. From his values, it is not possible to tell whether the anemia is hypochromic or macrocytic. Monkey 64, for instance, had "during deficiency" a red blood cell count of 2.4 million cells with 6.3 g. of hemoglobin, while monkey 80 had 2.3 million cells with only 4 g. of hemoglobin, and monkey 82 had 1.7 million cells with 8.0 g. of hemoglobin. Neither is it possible to tell whether these values represent average figures, the lowest levels reached, or whether

the two determinations were made on the same day. It would be interesting to know how promptly the anemia responded when riboflavin was added to the deficient ration. Several components of the vitamin B-complex, *i.e.* pyridoxine and "folic acid," influence bone marrow function. From Waisman's experiments it would appear that riboflavin also plays a role in this function. If satisfactory progress is to be made in understanding these relationships, however, the hematologic data describing the changes observed must be more complete and definitive than that provided in the present study.

GASTRIC SECRETION AND GASTRIC MUCOSA IN NUTRITIONAL DEFICIENCIES

It is often stated that the gastric mucosa in cases of pellagra is similar to that of the fiery red oral mucosa. The only recorded observations, however, are those of Schiff and Stevens (mentioned by Spies, Bean, and Ashe, *Ann. Int. Med.* **12**, *1830* (*1939*)) who described the appearance of the gastric mucosa of 2 patients. At autopsy, atrophy of the gastric mucosa has been reported (Spies and Payne, *J. Clin. Invest.* **12**, *229* (*1933*)).

The closest animal counterpart to human pellagra is canine blacktongue. For this reason, and because there is so little information in the literature regarding the appearance of the gastric mucosa in patients with pellagra, Layne and Carey (*Gastroenterology* **2**, *133* (*1944*)) made observations in 5 dogs. Blacktongue was produced nine times in these 5 animals by feeding them the well known diet of Goldberger and Wheeler. In three of the experiments the animals received weekly injections of 10 mg. of thiamin chloride. Gastroscopic examinations were made several times on these animals while they were receiving the standard laboratory diet before the start of the experiment. Three determinations of gastric secretion following the injection of histamine were also performed during the control period. After the start of the experiment, the dogs were examined gastroscopically at intervals from seven to fourteen days and gastric secretion was measured at intervals of seven to ten days. The dogs were maintained on the blacktongue-producing diet for periods of forty-nine to one hundred and two days and in all instances marked inflammation of the oral and pharyngeal mucosa, anorexia, and diarrhea developed. In three instances the animals were killed, while in the remaining experiments therapy was instituted and the gastroscopic observations and determinations of gastric secretion were continued until the animals had become normal.

It is noteworthy that hyperemia of the gastric mucosa was observed in seven of the nine experiments, but this was at all times mild and the reddening of the gastric mucosa subsided even though the inflammatory changes in the buccal mucosa became progressively more striking.

A change which was observed consistently was the development of a mild pallor of the gastric mucosa. This was observed in all but one of the experiments after the animals had been maintained on the blacktongue-producing diet for thirty or more days. This was accompanied by the development of anemia. At the same time the submucosal vessels of the stomach became more easily visible in the upper half of the stomach. The stomachs of these animals, furthermore, were distended easily and the mucosal folds disappeared when the stomach was only mildly inflated. It was assumed that the increased visibility of the submucosal vessels was probably caused by a decreased tonus of the wall of the stomach. This decreased muscular tone of the gastric wall was concomitant with loss of weight of the animals and consequently may have represented a

decrease of general muscular tone. As early as six or seven days after the institution of treatment, the tonus of the stomach returned to normal.

No constant or significant change in acid gastric secretion occurred in any of the experiments during the period of production of the disease, at the height of the development of the oral lesions of blacktongue, or following treatment with nicotinic acid. There was no difference between the findings in animals which received thiamin and those in the animals receiving no additional thiamin.

To the reviewer's knowledge, there have been no gastroscopic examinations in nutritionally deficient animals other than those done by these investigators, and their work is commendable. Studies of gastric secretion have been made, among others, by Gildea, Kattwinkel, and Castle (*New Engl. J. Med.* **202**, *523* (*1930*)) who found no change in acid gastric secretion in dogs given diets lacking various components of the vitamin B-complex. Miller and Rhoads (*J. Clin. Invest.* **14**, *153* (*1935*)) reported that achlorhydria occurred irregularly in canine blacktongue and they also described the development of gastric achlorhydria together with other changes in swine fed a deficient diet. The observations of Layne and Carey, however, must be given special weight because of their repeated, carefully controlled examinations.

There are certain pertinent differences between animal blacktongue and the human disease pellagra. One is that while both blacktongue and pellagra represent multiple nutritional deficiencies with special emphasis on nicotinic acid deficiency, the nature of the associated deficiencies may be somewhat different in the two instances. Furthermore, the human subject with pellagra probably suffers from a more prolonged deficiency than occurs in animal experiments developed over one and one-half to three and one-half months. Finally it must be pointed out that, although significant interference with acid gastric secretion has been reported in many cases of pellagra, there is no clear evidence that this is specifically due to a lack of nicotinic acid.

The significance of atrophic gastritis in relation to nutritional deficiency has been the subject of study by Shapiro and co-workers (*Gastroenterology* **2**, *121* (*1944*)). Noting that "atrophic gastritis" has been observed in pernicious anemia as well as in pellagra, sprue, and vitamin deficiency states in general, and in view of the reported disappearance of the abnormal gastroscopic findings in pernicious anemia under specific therapy, Shapiro and co-workers undertook a study of a group of patients in whom atrophic gastritis was found on gastroscopic examination. As criteria for this diagnosis they noted the presence of branching vessels, either bluish or reddish in color, frequently associated with lack of prominence or actual absence of rugae and a grayish or greenish-gray discoloration of the mucosa.

Thirteen patients with "uncomplicated" gastritis were investigated for evidence of nutritional deficiency. Two patients were found to have magenta colored tongues. In one there was diffuse atrophy of the papillae of the tongue, one had cheilosis, one complained of paresthesia, 5 had anemia, and in 3 of 6 patients whose small bowels were studied, there were small intestinal changes compatible with deficiency states. The diets of these patients, as viewed in relation to the recommended allowances of the National Research Council were deficient in about half the cases. Measurements of the urinary thiamin excretion, blood vitamin A, and carotene were interpreted as tending to confirm dietary history.

The investigators concluded that as compared with a control group of 10 patients, nutritional deficiency seemed somewhat more common in the patients with atrophic gastritis than in the control group. Shapiro and co-workers treated 5 patients having atrophic gastritis with large doses of thiamin, niacin-

amide, riboflavin, pantothenic acid, para-aminobenzoic acid, and vitamin A, but were unable to observe any significant changes in the gastric mucosa. In 2 of the subjects the atrophic changes disappeared at the same time that the patients were given choline chloride. The authors make no claim, however, that this represented cause and effect.

LEGUME PROTEINS

It has been generally assumed that legume proteins are inadequate in certain of the essential amino acids necessary for growth. In the past little differentiation has been made among the various legumes, nor has much attention been given to the effects of different methods of preparation. It is of considerable significance therefore to find from the work of Everson and Heckert (*J. Am. Dietet. Assn.* **20**, *81* (*1944*)) that the growth-promoting qualities of legumes seem to vary with the source, the degree of maturity of the seed, and the method of cooking used.

The biologic value of the various sources was judged by the gain in weight per gram of protein ingested by young male rats during an eight week period. Each diet supplied a 10 per cent level of protein. Casein, dried beef liver, peanut flour, and cottonseed flour were fed for comparison in amounts to furnish 10 per cent protein in the diet.

The vine-ripened (mature) seeds of navy beans, kidney beans, Lima beans, peas, soybeans, and pinto beans were tested both in the raw state and following heating in a pressure cooker at 15 pounds pressure for forty-five minutes. Green peas and Lima beans were tested in fresh form (immature) and following home drying, which was done by blanching and heating in an oven at 150°F. for approximately eight hours. Two samples of commercially-prepared, precooked navy beans (mature) were tested for their biologic value and compared with navy beans of the same source in the raw state and after having been heated in a pressure cooker at 15 pounds pressure for forty-five minutes.

The authors found that all of the mature legumes, except peas, were improved in biologic value by the heating procedures. In pinto beans, navy beans, and kidney beans, the beneficial effect was pronounced. With edible soybeans, heating increased the nutritive value from fair to an efficiency comparable to that observed for casein and beef liver. Everson, Steenbock, Cederquist, and Parsons (*J. Nutrition* **27**, *225* (*1944*)) have also studied the effect of germination, the stage of maturity, and the variety upon the nutritive value of soybean protein. They found no appreciable varietal differences in the Illini, Dunfield, Mansoy, Virginia Brown, and Mandarin varieties. All were greatly improved by heating. The protein of freshly germinated Illini beans was superior in nutritive value to the protein of the unheated mature beans. Immature soybeans likewise supplied protein of higher nutritive value than that of raw mature beans. The protein of germinated as well as of immature soybeans was improved by heating.

Everson and Heckert reported that mature heated Lima beans were also of high biologic value approaching closely that of soybeans. The poorest growth occurred when the protein was derived from the mature seed of peas. Furthermore, instead of being improved by heating, the mature peas were reduced in biologic value.

In contrast, the immature fresh green pea appeared to supply an unusually high grade of protein. Animals receiving this source of protein grew better than any group studied, even those fed casein and beef liver. When the fresh peas were blanched and dried at 150°F., the rate of growth was also superior, being only slightly lower than that produced by the pressure cooked soybeans, the casein, or the beef liver. The results on fresh peas

were rather unexpected since peas alone were not benefited by heating. The amount of heat involved in the five-minute blanching and subsequent drying at 150°F. seems to have lowered the growth-promoting properties slightly. These data suggest that for highest biologic value, fresh green peas should be preserved in a manner requiring the shortest possible heating periods. The short-time cooking period needed for frozen peas or fresh peas probably would not lower the biologic value unduly.

The proteins of immature green Lima beans did not support normal growth. However, drying this bean under home conditions resulted in a product in which the protein promoted superior growth equal to that of the mature seed heated at 15 pounds pressure for forty-five minutes. These data show that the use of heat is desirable if the highest biologic value is to be obtained from Lima bean proteins.

Two samples of raw mature navy beans failed to maintain rats longer than four weeks. Following heating at 15 pounds pressure for forty-five minutes, both samples served to permit a slow rate of growth; precooking definitely reduced the nutritive value of one sample while that of the second was slightly increased. It was thought possible that the length of the heating period employed in precooking might have varied sufficiently to account for the difference.

The rate of growth of animals receiving peanut meal and cottonseed meal in this study requires special comment as it was observed to be considerably lower than that of animals fed heated, vine-ripened soybeans, thus indicating a protein of lower nutritive value. These data are not in full agreement with the work of Jones and Divine (*Nutrition Reviews* **1**, *178 (1943)*) who reported much the same rate of growth for animals fed peanut flour, cottonseed flour, and soybean flour as the sole source of protein.

The authors point out that the number of samples reported in this study are too few to allow extensive generalizations. However, the data do reveal differences in the extent to which the nutritive value of legume protein can be affected by heat. The data also indicate that there is an appreciable difference in the growth-promoting qualities of various legumes, and that each source varies in biologic value depending upon the maturity of the seed.

EFFECT OF VITAMIN K ON EXPERIMENTAL HYPERTENSION

Interesting relationships have been suggested between nutritional elements and hypertension. Vitamin A preparations, for instance, were observed to cause striking reductions in the blood pressure of hypertensive dogs (*Nutrition Reviews* **1**, *20 (1942)*), although Wakerlin and associates later showed that the effective blood pressure-reducing factor was some unrecognized substance in the vitamin A preparation and not the vitamin itself (*Ibid.* **1**, *141 (1943)*). More recently Schwarz and Ziegler (*Proc. Soc. Exp. Biol. Med.* **55**, *160 (1944)*) have shown that parenteral administration of vitamin K to hypertensive rats also caused a significant lowering of the blood pressure.

The rationale for the use of vitamin K, being a quinone, is much better than it had been for vitamin A, and is dependent on the following observations: (1) Under anaerobic conditions, such as may exist in an ischemic kidney, amino acids can be decarboxylated without being deaminized; pressor amines, therefore, may accumulate (Holtz, Heise, and Lüdtke, *Arch. f. exper. Path. u. Pharmakol.* **191**, *87 (1938)*). (2) Acute renal hypertension has been produced by injection of the amino acid 1-dihydroxyphenylalanine

into the partially or completely ischemic kidney of the cat (Bing and Zucker, *J. Exp. Med.* **74**, *235* (*1941*)). The pressor effect is probably due to conversion of this amino acid to hydroxytyramine. Under conditions of normal renal blood flow, however, hypertension is not produced by the injection, presumably because amine oxidase destroys the pressor amine (hydroxytyramine). (3) Certain pressor amines can be inactivated by quinone precursors (Soloway and Oster, *Proc. Soc. Exp. Biol. Med.* **50**, *108* (*1942*)). Furthermore, four of ten quinones tested were shown to have blood pressure-lowering properties when given either orally or subcutaneously to rats with experimental renal hypertension (Friedman, Soloway, Marrus, and Oppenheimer (*Ibid.* **51**, *195* (*1942*)). Three of the effective four compounds were paraquinones while the fourth was a diorthoquinone. They had no effect on the blood pressure of normal nonhypertensive rats. Grollman and Harrison (*Ibid.* **52**, *162* (*1943*)) were able to confirm these results, and to show that fish body and liver oils contain a substance which is effective in reducing the blood pressure of hypertensive rats. They proved that the fish oil substance was not vitamin A and suggested that "it is possible that a quinone is formed by the oxidation of marine oils and that this is the agent responsible for the observed reduction in blood pressure." The above series of observations, therefore, not only explains the reason for testing the effect of vitamin K, a quinone, in experimental hypertension, but also gives a possible explanation for the observed depressor effect of certain vitamin A preparations.

Schwarz and Ziegler induced hypertension in rats by wrapping both kidneys with silk. The daily intramuscular injection of 5 to 10 mg. of 2-methyl-1,4-naphthoquinone dissolved in oil caused an average lowering of the systolic blood pressure of about 50 mm. Hg. (170 to 120 mm. Hg.). From the charted data, it appears that the depressor effect appeared within twenty-four hours and continued for the four days during which injections were made. After the administration of vitamin K was discontinued, the systolic pressure rose again to reach preinjection levels at the end of about ninety-six hours. A water soluble hydroquinone (2-methyl-1,4-naphthohydroquinone, disphosphoric acid ester tetrasodium salt) showed no pressure-reducing activity. The authors state that oil solutions of several other quinones were without effect; the oil, therefore, was not responsible for the activity of vitamin K (2-methyl-1,4-naphthoquinone).

These results are interesting and suggest therapeutic trial, under careful supervision, of vitamin K in human hypertension. The doses, however, will probably have to be much greater than those needed for the treatment of vitamin K deficiencies. It must not be assumed that the effect of vitamin K is any more specific than is that of other effective quinones, nor that one of the normal physiologic functions of vitamin K is to aid in the destruction of pressor amines. These relations probably have more pharmacologic than nutritional importance, but they cannot escape the attention of students of nutrition.

PATHOLOGY OF STAPHYLOCOCCUS ABSCESSES IN VITAMIN C DEFICIENT GUINEA PIGS

The literature contains many observations and discussions concerning the relationship of vitamin C deficiency to resistance to infection. The evidence, however, is contradictory. In regard to wound healing, much is known about the role of vitamin C and its

importance in reparative processes (*Nutrition Reviews* **1**, *305* (*1943*)). Strangely enough there has been no report of well controlled studies on the exact nature of local inflammatory reactions in vitamin C deficiency. Such a report by Meyer and Meyer (*Bull. Johns Hopkins Hosp.* **74**, *98* (*1944*)) supplies instructive observations.

Paired feeding experiments were carried out in guinea pigs receiving the same diet and differing only in that 15 mg. of pure l-ascorbic acid was given to the control animals each day. The diet was regarded as containing adequate supplies of protein, carbohydrate, fat, minerals, and all vitamins except vitamin C. After all animals had been fed the basal diet + ascorbic acid for two weeks, they were paired for sex and weight, paired feeding was started, and ascorbic acid was withdrawn from one member of each pair. Ten days afterward in the control and in the vitamin C deficient animals, abscesses were produced by inoculating intracutaneously on the abdomen a strain of hemolytic Staphylococcus aureus obtained from a large carbuncle. The animals were observed during life and careful histologic studies were made after death. Animals not receiving ascorbic acid developed typical signs of scurvy.

Although the lesions at the site of inoculation were about the same size in the control and in the deficient animals, in four to five days those in the control animals rounded up and became button-like. In sharp contrast, the lesions of the deficient animals remained soft and of cheesy consistency, and showed no evidence of demarcation from the surrounding tissue. The older lesions in the deficient animals when viewed from the peritoneal surface also showed grossly visible hemorrhage.

The histologic changes, which are well illustrated in the article discussed, were remarkably different in the two series of animals. In lesions examined twenty-four hours after inoculation, many more round cells were found at the periphery of the reaction in the control animals than in the deficient ones. Forty-eight hours later, in vitamin C deficient animals, only a few cells at the peripheral part of the reaction could definitely be distinguished as fibroblasts. There were many dilated capillaries, and free red blood cells were scattered around the areas where capillaries were in evidence. Instead of the relatively large number of polymorphonuclear cells seen in the lesions of the deficient animals, in the control animals the lesions showed at this time many more macrophages in the peripheral zone. While many capillaries were in evidence, there were no signs of free red blood cells or gross hemorrhage.

In the deficient animals eight days after inoculation, although the necrotic foci were localized, there was a wide peripheral zone of disorderly and loosely-arranged connective tissue. The breadth of the peripheral connective tissue reaction was out of all proportion to the size of the necrotic focus. The connective tissue cells were irregularly arranged, loosely spaced, and showed little cytoplasm. The interval between cells was taken up by a very faintly and unevenly stained material while nearer the center of the abscess there were lakes and columns of hyaline-like material. Many pigment containing macrophages were present at the border of the necrotic focus and many free red cells were scattered through the same area. In striking contrast was the orderly reaction in the control animals with its relatively narrower zone of connective tissue reaction, its dense wavy strands of normal-looking collagen with definite fibrillar structure, and tongues of granulation tissue invading the necrotic focus.

In later stages the same contrast was in evidence. Fourteen days after inoculation the histologic picture in the deficient animals showed even more evidence of disorderliness and ineffective reaction. At eighteen days the reaction about the necrotic tissue in the scorbutic animals was relatively huge as compared with that in the control animals

and both muscle layers as well as the skin were involved. Near the center of the abscess there were many free blood cells and pigment laden macrophages.

This study presents in a convincing way the striking difference between the reaction in scorbutic and in nondeficient guinea pigs. In the scorbutic animals it appeared that in the initial reaction surrounding the site of inoculation, the appearance of macrophages was delayed and the total number was less than normal. Although the polymorphonuclear reaction was prompt and proportionate, phagocytosis seemed less effective after a few days than was normal. As in the healing of sterile incisions, proliferation of fibroblasts continued much longer than in control animals and no normal collagen was formed. The necrotic centers of the abscesses were not well walled off and the arrangement of the connective tissue was disorderly. The importance of ascorbic acid was obvious. To what extent lack of this vitamin influences healing of infectious processes in man, however, is still a matter of surmise.

ROLE OF SERINE IN THE BIOSYNTHESIS AND BREAKDOWN OF TRYPTOPHANE

Increasing attention is directed to the special metabolic function of the amino acids apart from their status as building units in protein synthesis. Recently serine has been shown to play a special role both in animal tissue and in microorganisms. In 1942 Binkley and du Vigneaud (*J. Biol. Chem.* **144**, *507* (*1942*)) found that serine is a necessary component in the formation of cysteine from homocysteine in animal tissue. They proposed that the β-hydroxyl group in serine may react with the sulfhydryl group of homocysteine, forming a thio-ether which is subsequently converted to cysteine and homoserine. More recently, the biologic reactivity of the hydroxyl group of serine has been illustrated in another reaction in some interesting experiments by Tatum and Bonner (*Proc. Nat. Acad. Sci.* **30**, *30* (*1944*)). They found that the biosynthesis of tryptophane by certain microorganisms takes place through a direct reaction between indole and serine.

The microorganism used was a certain strain of the mold Neurospora crassa. This strain, which is a mutant produced by x-ray radiation of Neurospora, reported by Beadle and Tatum (*Proc. Nat. Acad. Sci.* **27**, *499* (*1941*)), requires indole for growth.

Experiments were carried out both with actively growing cultures and with mycelium in non-nutrient media. Indole was added and the disappearance of this substance was followed in the presence of various amino acids and sugars. It was noted that indole added to a Neurospora culture disappeared rather slowly, but that the addition of serine causes a marked increase in its consumption. The action of serine is apparently specific for the l(-) compound since it was twice as active as the dl compound, and the amount of indole consumed proved to be a function of the l(-) serine concentration. The authors, furthermore, have shown that the indole taken up is converted into tryptophane. When the mycelium was incubated two days with 50 mg. of indole and 500 mg. of serine in 1 liter of water, all the indole disappeared and tryptophane was formed in amounts equivalent to 30 to 50 per cent of the indole consumed.

The formation of tryptophane was demonstrated both by the colorimetric method of Woods and by isolation of the crystalline racemic acetyl dl-tryptophane. These two methods do not distinguish between d and l tryptophane. The results of a biologic assay on a strain of Neurospora showed, however, that the l(-) form of tryptophane had been synthesized during the incubation with indole and l(-) serine.

The biologic synthesis of l(-) tryptophane

from l(-) serine and indole is probably a direct reaction between indole and l(-) serine. The authors stress the structural relationship of serine to the side chain of tryptophane, the specificity of serine in the reaction, and the failure to detect tryptophane in an incubation mixture with indole or serine alone.

If l(-) tryptophane is added to a culture of Neurospora, part of the amino acid is broken down to indole acetic acid, but so far no formation of indole has been observed. It is, however, a well known fact that cultures of Escherichia coli form indole from tryptophane, and in this case Tatum and Bonner have presented experiments which strongly suggest that serine is a product of this reaction. They found that the formation of indole from tryptophane by E. coli was specifically inhibited by addition of serine. Thus, in 50 ml. volume of a suspension of E. coli (about 20 mg.) containing 2 mg. of l(-) tryptophane, addition of 10 mg. of dl-serine decreased the rate of indole production to half.

This latter observation may not be without practical significance. The coli bacteria in the intestinal tract form indole and skatole, cyclic amines which are toxic for the animal organism and which are detoxified in the liver. If the rate of formation of these compounds exceeds the rate of detoxification, they accumulate in the organism and give rise to toxic symptoms, particularly of the brain. If serine could be administered in such a way that it would not be released until it reached the colon, it might exert an inhibitory effect on the formation of indole by the coli bacteria.

SECONDARY PELLAGRA

While at present much attention is focused on the production of disease by malnutrition because of the ravages of war, famine, and mass starvation, still the production of malnutrition by disease remains a problem frequently encountered by the discerning physician. Furthermore, an examination of the background of disease as an obstacle to proper nutrition may throw light on some poorly understood aspects of the pathogenesis of certain deficiency diseases. Toward this end, the review of secondary pellagra by Bean, Spies, and Blankenhorn (*Medicine* **23**, *1 (1944)*), in which the authors' experience, extending over more than a decade, is presented against the background of a comprehensive review of the literature, is of unusual interest. Its value is enhanced because the observations were made in a region where pellagra is generally believed to be uncommon, as well as in an endemic pellagra area.

The ideal criteria for classifying a case of pellagra as "secondary" are satisfied with the demonstration that: "(1) the patient ingested a diet adequate for his ordinary needs, or at least not permitting a recognizable deficiency; (2) some extraneous condition occurred which was followed by the development of pellagra while the same diet was consumed; and (3) when the underlying condition was corrected, pellagra disappeared." As these demands cannot be satisfied when the provoking factor cannot be removed or when the pellagra is treated with specific therapy or undergoes spontaneous remission, many cases are included on circumstantial evidence of their secondary nature. It is often impossible to allocate the relative importance of a deficient diet and some disease process when both have existed prior to the development of pellagra.

Only cases which presented characteristic pellagrous glossitis and symmetrical dermatitis at the time of observation are included. The cases are drawn from the authors' experience in Ohio from 1930 to 1939, first at the University Hospitals in Cleveland and later at the Cincinnati General Hospital,

and from their observations at the Hillman Hospital in Birmingham, Alabama, during 1940 and 1941. From the Ohio total of 278 cases of pellagra, 146 were classed as secondary, while 242 secondary cases are in the series from Alabama, comprising one-fourth or less of the entire group of pellagrins seen there. No statistical analysis is made as the groups are not strictly comparable and could not be regarded as representative samples of the populations from which they were drawn. It is of interest that the Ohio subjects were about equally divided according to race (69 white to 77 Negro) without much difference according to sex among the whites, but with 56 of the Negro subjects being females. In contrast, only 22 of the Alabama cases were observed in Negro subjects, and 171 of the 242 cases were seen in white females.

With present knowledge of the role of B-complex vitamins in normal cellular economy, the authors believe that the problem of even secondary pellagra is essentially one of the balance between supply and demand, and logically divide the discussion according to decreased supply of vitamins due to obstruction along the path of intake, or to increased loss, or to an elevation of the requirement to supply increased needs. A tentative outline of mechanisms by which disease of the alimentary tract, the classic cause of secondary pellagra, may operate to produce the deficiency disease, lists increased intestinal motility, decreased enzymatic digestion of food, inadequate absorption, abnormal bacterial flora, destruction of vitamins and their inactivation by dietary constituents, defect in phosphorylation, liver damage impairing storage and utilization, as well as loss of appetite, nausea, vomiting, and other mechanical factors.

In this series, disease of the alimentary canal was the principal factor in 98 cases, accounting for 32 per cent of the Ohio cases and 22 per cent of the Alabama cases. In 42 additional patients it was an accessory contributing factor. Attention is called to the part played by defective teeth or adentia in necessitating diet changes due to impairment of mastication. In 9 of the Alabama pellagrins adentia was the underlying factor. A total of 22 cases had disease of the mouth or throat as the principal cause of pellagra. It is of interest that these acted largely by causing dysphagia or obstruction to food intake; the belief that cancer of the tongue is often preceded by some vitamin B-complex deficiency receives no support from this clinical study. Disease of the stomach appeared to be the basic cause in 20 cases, 8 of these in patients with peptic ulcer, and 4 with gastric carcinoma, 3 with old gastroenterostomies, and 5 classified as gastric neurosis. The chronic dysenteries accounted for 11 cases, 4 being due to bacillary infection, 1 to amebas, and 6 to nonspecific ulcerative colitis. Of the 27 cases attributed to rectal disease, 11 were due to rectal strictures; the lesion is stated to be nearly always a result of lymphopathia venereum and nearly all reported victims have been Negro females. In 6 cases hemorrhoids, particularly when there had been severe hemorrhages and operations interfering with sphincter control, seemed to be the most important predisposing cause of the pellagra. Intestinal parasites were important factors in only 4 cases.

Seventeen cases of pellagra along with cirrhosis of the liver were observed, 15 in the Ohio group where they accounted for 6 per cent of all pellagra and 11 per cent of the secondary cases. This is contrasted with its occurrence in less than 1 per cent of all pellagrins in the endemic area. In a discussion of the possibility that cirrhosis itself may be the result of dietary deficiency, it is pointed out that the rarity of cirrhosis as the terminal event in the life of an endemic pellagrin makes it improbable that cirrhosis is caused by the same deficiencies which cause pellagra. There were 4 additional cases where gallbladder disease was the main contributing cause of the pellagra.

Pellagra developed shortly after operation

20 times and in 10 additional cases operation was an important complicating agent. It was twice as frequent in the Alabama as in the Ohio group. The operative procedures involved were on the female genital system in 13 cases and on the alimentary tract in 15 instances. Factors conducive to the post-operative development of pellagra are many. Among these are the depletion of body stores by the disease process for which surgery was done, the blockage of food intake immediately after operation by anorexia, nausea, vomiting, gaseous distention, the use of gastric suction, and the parenteral administration of dextrose. Pellagra was observed 5 times following irradiation therapy.

Infections were considered the major precipitating cause of pellagra in 74 cases, accounting for 18 per cent of the Ohio group and 19 per cent of the Alabama subjects. It was an accessory contributing factor in 53 cases. Pneumonia led the list with 18 cases, 12 of them in the Ohio group with Negro males strongly represented. Pulmonary tuberculosis accounted for 6 cases, all Negroes in the Ohio group, and other chronic pulmonary infections for 4. Malaria, usually untreated or inadequately treated, was the chief factor in 13 cases, all in Alabama. Seven cases were secondary to influenza, 6 from the Alabama series. Pellagra followed the childhood diseases of whooping cough, mumps, and measles 9 times; 8 of these were in the endemic pellagra region. Chronic pelvic inflammatory disease was a principal factor in only 4 cases, but an accessory factor in 11 more. The frequency of other pelvic disease in pellagrins is pointed out. The authors indicate that "non-specific factors impeding nutrition, and those accelerating general metabolism and tissue respiration suffice as an explanation for the disastrous nutritional sequels to infections and fevers."

The drain of pregnancy and lactation on the maternal organism is emphasized as being the important precipitating factor in 90 cases, all but one occurring in white mothers in the region where pellagra is endemic. In a selected series of 290 women over 20 years of age seen in the Birmingham clinic with severe or moderately severe vitamin deficiency diseases, pregnancy, parturition, and lactation were of importance in only 13 per cent of the Negro women but was the most important cause in 32 per cent of the cases of all pellagra seen in white women and probably a predisposing handicap in the majority. It was further observed that an outbreak of pellagra was more likely to occur if the last trimester of pregnancy coincided with the seasonal peak of the disease, and that the risk of relapse was greater with each succeeding pregnancy and period of lactation. The authors note that "contrary to a widespread belief these pellagrins were remarkably fertile."

Various forms of heart disease, usually with congestive failure, accounted for 32 cases of secondary pellagra, 27 of them from the Ohio patients and with a marked preponderance of Negro females. Hypertension and coronary artery disease were the leading etiologic diagnoses in the cases developing complicating deficiency disease. Among the possible mechanisms involved in the production of pellagra in heart disease are mentioned dietary restriction, self-imposed or prescribed, digitalis intoxication, increase in metabolism, and possibly the disruption of intracellular processes by tissue anoxemia.

Among the endocrine disorders, pellagra was observed secondary to Addison's disease in 4 cases, to diabetes mellitus 3 times, hyperthyroidism 3 times, in myxedema once in an untreated case and once during thyroid administration. The inadequacy of present knowledge concerning the interrelationship of vitamins and hormones in man is emphasized. Of interest is the observation that the administration of 3 to 6 grains of thyroid substance daily to a group of 89 ambulatory patients in Birmingham during a four to eight week period when their pellagra was quiescent was followed by relapse in only a few more instances than in a control group.

Among the other disease processes that were the principal causes of secondary pellagra in more than a few instances were 8 cases of nonalimentary tract neoplasm and 6 cases of bronchial asthma. In 8 cases the deficiency disease followed acute hemorrhage. Drugs seemed to be a factor only in cases of addiction.

The variations in the pattern of provoking disease suggest significant differences in the two regions. Pellagra often followed trivial sickness in Alabama whereas in the Ohio municipal hospitals it resulted from more severe and disabling diseases. More than any other factor, childbearing and its sequelae predispose the vulnerable segment of the population where the diet is near the borderline of adequacy. The bearing of the dietary background of the patient in avoiding postoperative deficiency disease is important.

Spies and associates have repeatedly pointed out that what is seen and recognized as pellagra, like the visible part of an iceberg, indicates a much greater and widespread subsurface danger. Their experience reported in this review gives strong support to the belief that malnutrition of a serious nature is more prevalent than a survey of frank deficiency disease indicates.

VITAMIN A ABSORPTION IN CASES OF PROTOZOAN INFESTATION

It has never been established that infestation by the protozoan parasite Giardia lamblia has any harmful effects in man. This parasite is found in the stools and duodenal contents and may be associated with symptoms so varied and so vague that it has been difficult to be certain that they were caused by the parasite. It is true that eradication of the parasite has sometimes been associated with disappearance of symptoms, but many times results have been such as to leave room for doubt. Objective evidence of benefit derived from eradication of the parasite has been lacking.

Véghelyi (*Am. J. Dis. Child.* **59**, *793 (1940)*) noted an increased amount of fat and lipase in the stools of children harboring Giardia lamblia and concluded that the parasite impaired the absorption of fat from the intestines. Katsampes, McCoord, and Phillips (*Am. J. Dis. Child.* **67**, *189 (1944)*) have reported observations indicating that the absorption of vitamin A is impaired by the presence of this parasite in the bowel.

Using the vitamin A absorption test of Chesney and McCoord (*Proc. Soc. Exp. Biol. Med.* **31**, *887 (1934)*), 15 cases were studied before and after eradication of the parasite. The absorption of the vitamin in infected patients, while variable, was less than normal in all instances and poor in at least half of them. The absorption curves in the same patients after treatment were very much improved, although in about a third of the patients the improvement was not remarkable at first. The authors were careful to demonstrate that the administration of quinacrine hydrochloride, the drug used to eradicate the parasite, does not itself cause improved absorption of vitamin A. This was done by comparing vitamin A absorption before and after administration of the drug in 3 patients with celiac disease, who were free from giardiasis.

These observations, then, lend confirmation to the suspicion that infestation with Giardia lamblia has harmful effects in man.

FURTHER OBSERVATIONS ON VITAMIN E DEFICIENCY

Loss of fertility associated with vitamin E deficiency and testicular degeneration has thus far been demonstrated only in the rat. Studies in mice on vitamin E deficient diets

have failed to reveal this effect (Bryan and Mason, *Am. J. Physiol.* **131**, *263* (*1940*)), and in the rabbit muscular dystrophy occurs in the absence of testicular degeneration (Mackenzie and McCollum, *Proc. Soc. Exp. Biol. Med.* **47**, *148* (*1941*)). Likewise in guinea pigs muscular dystrophy occurs as the first and most striking manifestation of vitamin E deficiency. Pappenheimer and Schogoleff (*Am. J. Path.* **20**, *239* (*1944*)) have found, however, that early degenerative changes in the testicles could be demonstrated in guinea pigs maintained for as long as one hundred thirty days on a vitamin E deficient diet. In one animal killed on the hundred seventy fifth day, advanced degeneration was found.

In another article, Kaunitz, Pappenheimer, and Schogoleff (*Am. J. Path.* **20**, *247* (*1944*)) present data which indicate that a single small dose of tocopherol given to young rats on vitamin E deficient diets during the late nursing period will significantly delay the onset of testicular degeneration. Thus they observed that a single dose of 0.5 or 1.0 mg. of dl-alpha-tocopherol acetate given on the fifteenth day of life produces a significant retardation of postpubertal testicular degeneration in rats maintained on a vitamin E deficient diet. Administration of 5 mg. at this time produces a still greater protective effect. It is noteworthy, however, that the administration of 1 mg. on the sixth to eighth day was without effect. Giving this amount after weaning, that is during the twenty-ninth and thirtieth day, afforded less protection than when 1 mg. was given on the fifteenth day. These data suggest that a deficiency of vitamin E during the third week is of critical import.

Since even a small dose of tocopherol given in the late nursing period delays the onset of testicular degeneration, it is possible that the late appearance of this degeneration in the earlier experiments was due to the fact that these animals were suckled by mothers on a stock diet containing vitamin E. The investigators are seeking further information on this point and on the occurrence of the responsible factor in milk.

VITAMIN C AND NEUROMUSCULAR REGENERATION

Considerable support can be assembled for the idea that vitamin C is important in the healing of wounds in man or in the guinea pig (*Nutrition Reviews* **1**, *98* (*1943*)), but relatively little information is available on the role of the vitamin in the regeneration of nerve or muscle. Hojer (1924) and Dalldorf (1929) have both observed muscle damage in experimental animals with severe scurvy, while Kodicek and Murray (*Nature* **151**, *395* (*1943*)) reported swellings in the muscle and an overgrowth of connective tissue following injury to the bone and muscle of guinea pigs fed diets partially deficient in vitamin C.

Recently Hines, Lazere, Thomson, and Cretzmeyer (*J. Nutrition* **27**, *303* (*1944*)) have studied the effect of a suboptimal intake of the vitamin upon the regeneration of nerve and muscle after a peripheral nerve injury. The experimental procedure was essentially that employed in their studies on alpha-tocopherol and neuromuscular regeneration (*Nutrition Reviews* **1**, *414* (*1943*)). Fifty young guinea pigs were fed the Eddy ration low in vitamin C plus daily supplements of 0.5, 1.0, 2.5, 5.0, or 50 mg. of ascorbic acid given by pipet. A few days were allowed for the animals to become accustomed to the ration, when one gastrocnemius muscle was denervated by exposing the tibial nerve under anesthesia and crushed with a heavy linen ligature against a brass rod. The untreated contralateral muscle and nerves served as controls.

The gastrocnemius muscle of the guinea pig loses about one third of its mass and three fourths of its original strength during

the first two weeks following denervation. Soon thereafter, the first signs of reinnervation appear, atrophy is checked, and the affected muscles gradually recover mass and strength. After thirty-five days it can be demonstrated that the regenerating nerves have established functional contact with their muscles, and this time-interval was chosen for determining the degree of recovery on the different intakes of ascorbic acid. The strength of the muscles was determined by measuring the maximal isometric tension developed when volleys of slightly supermaximal stimuli were applied either to the muscle directly or to the nerve activating it. It had been noted previously by Hines, Thomson, and Lazere (*Am. J. Physiol.* **137,** *527 (1942)*) that in normal muscle the same tension developed whether the stimulus was applied to the muscle directly or to its activating nerve. However, in denervated muscle much weaker responses were noted when the stimulus was applied to the nerve than to the muscle, but as the regeneration of the nerve progressed, the two responses became more nearly equal.

In the present experiment the nondenervated control muscles showed essentially the same strength at all levels of vitamin C intake from 0.5 to 50 mg. per day, whether the stimulus was applied to the nerve or to the muscle. However, when no vitamin C was fed for twenty days, muscular strength decreased by 17 per cent. After thirty-five days the denervated muscles were weaker than normal at all levels of vitamin C intake, but the degree of weakness, or conversely the extent of regeneration, depended directly upon the amount of vitamin C ingested. Increases in the consumption of the vitamin from 0.5 to 2.5 mg. per guinea pig daily resulted in corresponding increases in muscle strength. Above this level no further improvement was noted when the stimulus was applied directly to the muscle, and only slight improvement when the stimulus was applied to the regenerating nerve. As might be expected the responses to the nerve were weaker than the responses to the muscle itself, since regeneration of the nerve was incomplete at all levels of vitamin intake.

The findings are interpreted to indicate that the regeneration process is impaired when the consumption of vitamin C is below the optimal level for growth and protection against scurvy, but that no great beneficial effect results from the consumption of a large excess of the vitamin. No attempt was made to ascribe a direct role of the vitamin in either nerve or muscle tissue. The technic of denervation employed deprives the muscle of both sensory and motor innervation, with a loss of protective reflexes, thus making the muscles more vulnerable to stress, strain, and trauma. Any deficiency in collagenous intercellular substances in the supporting tissues therefore, would also contribute to retarded recovery. It is, however, of interest that numerous capillary hemorrhages were observed in the regenerating muscles of guinea pigs receiving the lower levels of ascorbic acid. Such hemorrhages were absent in the corresponding normal muscles of the same animals, nor were hemorrhages present in the regenerating muscles of the pigs receiving the larger amounts of vitamin. This might imply a greater need for vitamin C by the regenerating tissues. Certainly every precaution should be taken to ensure an adequate supply of vitamin C to individuals recovering from nerve or muscle injury.

THE NUTRITIONAL REQUIREMENTS IN INANITION

Our knowledge of nutritional requirements is based chiefly on the needs for growth and maintenance. Less is known about the nutritional requirements in states

of inanition, whether associated with some disease or caused by poverty or the deprivations of war. A fuller knowledge regarding the body's method of adjustment to conditions of insufficiency is needed. One example of such an adjustment is the observation that in occasional subjects receiving a diet lacking in thiamin, this vitamin can be derived from bacterial synthesis in the bowel (Najjar and Holt, *J. Am. Med. Assn.* **123,** *683 (1943)*).

Holt and Kajdi (*Bull. Johns Hopkins Hosp.* **74,** *121 (1944)*) report some observations pertinent to these questions. Their experiments in rats are based on the assumption that under given conditions of dietary restriction the ability of single foodstuffs to prolong survival or to produce benefit indicate a need for such foodstuff. It is assumed that in inanition states the rat will eat what he can use, and that his survival will indicate his need of particular foods made available to him.

The first experiment was designed to compare the ability of carbohydrate, fat, and protein to prolong survival. Rats 30 to 35 days of age weighing about 65 g. were given glucose, olive oil, or casein ad libitum as well as water. It was found that rats on glucose survived an average of twenty-seven days and those given olive oil survived the same length of time. In striking contrast was the fact that casein supported life for an average of only eight and a half days. It was noted that rats suddenly shifted from a mixed diet to a diet of pure fat or carbohydrate seldom consumed their entire caloric requirement from the single foodstuff on the first or even the second day of the new diet. Only after three or four days did the food intake rise to a maximum and fairly adequate intake. After about five days, however, the food intake began to decline, decreasing steadily until the death of the animal. In the animals given only casein the rise in food intake never took place.

Assuming that the adaptation to a high protein intake is a more difficult matter for the animal to accomplish than the adaptation to a high fat or carbohydrate diet, the experiments were repeated on larger animals with greater food reserves. In rats of 150 to 250 g. weight, survival on casein was twice as long as on fat or carbohydrate. It thus appears that if the rat is given time to adapt himself to an all protein diet the superiority of that diet becomes apparent. It was also found in another experiment that when small rats of 65 g. weight were adapted to a high protein diet by gradually increasing the proportion of protein in their food, it was possible to increase their survival time on casein alone from an average of eight and a half days to an average of seventeen and two-tenths days. It was noted in these studies that the intake of water was much higher when the diet contained protein alone than when it consisted of carbohydrate or of fat. On the last mentioned diet the water intake was minimal.

The time needed for adaptation to a protein diet can be explained by the hypertrophy of the liver and kidney required to accomplish the additional deamination and urea excretion necessitated by the protein increment (Osborne, Mendel, Park, and Winternitz, *J. Biol. Chem.* **71,** *317 (1927)*). The greater need for water is explained by the increased quantity of urea to be excreted. Carbohydrate was found to require an amount of water intermediate between fat and protein. The authors suggest that this is explained by the greater physical activity of animals on a carbohydrate diet as compared with those receiving only fat.

Observations were also made on the value of various carbohydrates for survival. Rats receiving levulose, dextrose, invert sugar, sucrose, and maltose survived the same length of time. Those receiving xylose, sorbose, sorbitol, mannitol, and pentaerythritol showed a distinctly inferior performance, as did animals receiving lactose and galactose.

A similar comparison of various types of fat showed lard, olive oil, and linseed oil to

give longest periods of survival whereas corn oil, coconut oil, peanut oil, and cod liver oil were less effective. At the bottom of the list were sesame oil and rape seed oil. A number of the fats permitting only short survival periods were noted as containing appreciable quantities of fatty acids that are not readily assimilable.

Reference has already been made to the rapid increase in food intake to a maximum when rats were shifted from a stock diet to one of carbohydrate or of fat alone, and the subsequent decline in food intake which continued steadily until the death of the animal. It was thought that the increase in food intake during the early days of the single food diet might well be the time required for the animal to adapt himself to the new diet, but the subsequent failure of appetite suggested the development of some deficiency which no longer permitted the animal to utilize the food in the quantities he had previously been able to handle. The development of a deficiency of this sort is also suggested by the observation that starved animals invariably contain some subcutaneous fat and a considerable quantity of dispensable tissue protein that could have been used to supply energy had not some other mechanism failed. Seeking to find the nature of this limiting factor Holt and Kajdi in a second paper (*Bull. Johns Hopkins Hosp.* **74,** *142 (1944)*) tested the value of the addition of 3 per cent sodium chloride solution or of a complete mineral mixture to a pure glucose diet. No improvement in survival was noted. The B-vitamins were then studied by adding to the glucose diet thiamin, riboflavin, and nicotinic acid singly or in combinations. As might be expected, the addition of thiamin to the diet of glucose produced a substantial prolongation of survival, an average of forty-nine and eight-tenths days as contrasted with twenty-seven and three-tenths days. Riboflavin alone was of no value. The addition of nicotinic acid alone caused a slight and possibly significant increase in survival. Multiple B factors including pyridoxine, filtrate factor concentrate, and the yeast extract vegex produced no longer survival than that associated with the addition of thiamin alone.

A similar study of the value of fat soluble vitamins in prolonging survival on an olive oil diet indicated no appreciable benefit. The addition of thiamin to olive oil alone was associated with a slightly longer survival period, possibly due to the need of this vitamin for the conversion of the glycerin fraction of fat into sugar. Riboflavin added to a diet of olive oil alone offered no advantage.

These studies mark only a beginning in the attempt to answer a problem which will require much more investigation. The increasing use of parenteral administration of food substances in various medical and surgical diseases of the gastrointestinal tract make it particularly important to know in what ways these observations of Holt and Kajdi apply to man.

NICOTINIC ACID

Nicotinic acid was first synthesized by the organic chemist about seventy-five years ago. It was isolated from natural products a few years later. However, for many years after that the compound remained on the chemists' shelves with little attention. In 1934 nicotinamide, a close derivative, was found as a hydrolysis product of two co-enzymes. This led to an active interest in the biochemistry of nicotinic acid. Within a few years (1937) it was established as an essential growth factor for Staphylococcus aureus, and a short time later it was found to prevent the deficiency disease black-tongue in the dog. Subsequent clinical trials soon showed that the long sought

pellagra preventive factor was nicotinic acid, and quantities of the synthetic vitamin became immediately available. It is estimated that 400,000 pounds of nicotinic acid were manufactured in 1943 for therapeutic use and for the enrichment of foods. In the meantime, rapid advance in the knowledge of the chemistry and biochemistry of nicotinic acid and related compounds has occurred. Elvehjem and Teply (*Chem. Reviews* **33,** *185 (1943)*) have reviewed the subject in a concise and complete manner. For details including bibliography, the reader is referred to the original publication.

Nicotinic acid, unlike several of the other vitamins, is unusually stable. It is not destroyed by boiling with acid or alkali. Therefore, losses resulting from processing or preparing food are small unless cooking water or juices, which readily leach out significant quantities, are discarded.

Nicotinic acid in the form of the amide occurs widely distributed, particularly in yeast and meat, as part of the structure of two coenzymes. They are referred to as coenzyme I and coenzyme II, and contain in addition to nicotinamide, two sugar groups, adenine, and phosphate groups, and differ in structure only in that coenzyme II contains an extra phosphate group. Thus, although both coenzymes are similar and serve as parts of enzyme systems, the function of which is to make the energy of certain metabolites available for use of the cell, they each show distinct specificities as to the particular metabolites with which they react. The structures of the two coenzymes have been determined and many of the reactions in which they are involved are now known.

Nicotinic acid has been shown to be a nutritive essential for man, dogs, chicks, monkeys, and many forms of bacteria. However, some species such as the rat seem able to synthesize the compound and, therefore, do not need it in their diet. While most organisms can use either the free acid or the amide to synthesize their coenzymes, Haemophilus influenzae and a few other organisms are exceptions in that they require the preformed coenzyme in the culture medium. This characteristic of H. influenzae has been used in the development of a microbiologic method for the measurement of coenzymes I and II in tissues. Other organisms, i.e., Lactobacillus arabinosus, have been utilized in a similar method for the assay of total nicotinic acid in tissues and foods. Culture medias containing all materials necessary for growth of the particular organism except the coenzyme or nicotinic acid are prepared. The extent of growth or growth products developing in such a media upon inoculation will depend on the amount of nicotinic acid or coenzyme added in the extracts to be tested. By the use of such methods combined with more conventional analytical procedures, the distribution of coenzyme and nicotinic acid in the tissues of both normal and deficient subjects have been studied. It has been shown that the coenzyme content of liver and muscle decreases with deficiency; however, little change occurs in the brain and kidney. All agree that the coenzyme content of red blood cells can be temporarily increased by ingestion of large doses of nicotinic acid and that the decrease during deficiency is only slight. "It has been concluded that there is no diagnostic value to be obtained from determinations of coenzymes in borderline cases of deficiency." Thus pellagra appears to be a more complicated process than just a general tissue decrease in coenzymes.

Knowledge of the metabolism of nicotinic acid is very incomplete. In man its excretion is primarily in the form of the inactive trigonelline (also present in certain foods), but small quantities of nicotinuric acid, nicotinic acid, and other as yet unidentified products also appear. The nature and proportions of the excretion products vary with the species and the nicotinic acid

intake. While in general the amounts of certain excretory products are indicative of the nicotinic acid status of the subject, more knowledge is required before exact interpretation in terms of nutrition can be made. On high levels of intake all the vitamin cannot be accounted for in the urine. It is apparent that the metabolism is complex.

Both microbiologic and chemical methods have been used for food analysis. Although there still remain many difficulties and uncertainties in the general application of these methods, they are sufficiently practical and accurate for many purposes, and data on food values are accumulating steadily.

A large number of derivatives of nicotinic acid and similar compounds have been tested for biologic activity in man, animals, and bacteria. With few exceptions, compounds found active for one organism will also suffice for others. Nicotinic acid, nicotinic acid esters, the amides and substituted amides have been found active. It will be noted that these are all compounds which can be hydrolyzed to the free acid by the organism. However, β-picoline and a few other compounds which are capable of oxidative conversion to nicotinic acid have been found slightly active. Changes in position of the acid group in the pyridine ring lead to inactivity, as does the addition of other groups to the ring. In other words, the structure of nicotinic acid shows a high degree of biologic specificity.

FOOD COMPOSITION

Nutritional accounting of the food intake of individuals and groups has been based upon various tables of food composition Widdowson and McCance (see *Nutrition Reviews* **1,** *306 (1943)*) have pointed out that there are two extreme schools of thought about food tables: "One tends to regard the figures in them as having the accuracy of atomic weight determinations; the other dismisses them as valueless on the ground that a foodstuff may be so modified by the soil, the season or its rate of growth that no figure can be a reliable guide to its composition. The truth, of course, lies somewhere between these points of view." Numerous comparisons have been made of the determined versus the calculated values as obtained from various food tables. Young and McHenry (*Canad. Pub. Health J.* **33,** *224 (1942)*) and Patterson and McHenry (*Ibid.* **32,** *362 (1941)*) found considerable discrepancy existing between the calculated nutritive values as taken from various food tables and the determined amounts of calories, protein, fat, and ascorbic acid. Still greater variation exists in the tables of nutritive values of the vitamin B-complex. With the development of improved methods of assay, it has become necessary to evaluate methods used before selecting data. Furthermore, gaps exist in data as concerns the effects of preparation and storage on food composition. As a result considerable confusion exists in the selection of average or representative values suitable for use in dietary evaluations.

In order to meet the need for assembling, coordinating, and appraising data on food composition, the Office of the Quartermaster General of the War Department requested the Food and Nutrition Board of the National Research Council to establish a committee. Dr. C. A. Elvehjem was appointed chairman and Dr. Paul Pavcek, secretary. Experts from this country and abroad have participated in the work. The committee has not been satisfied with published data but has collected unpublished data which are on record in various laboratories. In addition, the committee has correlated and planned experiments where further data were needed. Recent accomplishments of

this committee have been reported by Pavcek and Elvejhem (*J. Am. Dietet. Assn.* **20,** *216 (1944)*). In order to compare the results of various methods of assay, several collaborative vitamin assay studies have been sponsored. The first series indicated a favorable comparison between biologic thiochrome, fermentometer, and fungus growth methods for the determination of thiamin. Excellent agreement was found in comparative analyses for ascorbic acid using the phenylhydrazine method and the indophenol method.

Considerable effort has been expended in obtaining results indicating the effects of processing, preparation, and storage on the nutritive values. The Army C and K rations have been completely analyzed and on the basis of this, certain changes, notably in the thiamin content of the biscuit components, are contemplated. Complete data have been obtained on storage losses of thiamin and riboflavin in the K ration. These studies indicate that as much as 60 per cent of the thiamin is lost during storage at 104°F. for four months. These studies and the joint studies at the University of Chicago and Wisconsin indicate that on dehydrated pork and beef, riboflavin and niacin losses are negligible, even after storage at 135°F. for two hundred eighty-four days.

The paucity of data on the vitamin content of commercially produced dehydrated vegetables and dehydrated soups was noted. The Committee on Food Composition agreed to assemble this information and sent out 100 samples to various participating laboratories. Analyses have been made of dehydrated white potatoes, sweet potatoes, onions, cabbage, carrots, beets, cranberries, tomato juice cocktail, apple nuggets, and navy bean, yellow pea, and green pea soups. As a supplement to the survey on dehydrated vegetables, various special methods of dehydration have been considered such as the use of infra-red, electronic radiation, flue gases or products of combustion, and vacuum dehydration. A recent development by Godfrey L. Cabot, Inc., Boston, involves the use of heated natural gas as the dehydration atmosphere. The high vitamin C retention in cabbage and potatoes reported for this process has been checked on numerous samples both by the indophenol and phenylhydrazine methods.

Recently the committee has correlated and planned experiments on losses of nutrients during the cooking of foods. The problem of losses of nutrients in institutional and restaurant cooking was assigned to the Committee on Food Composition. Previously, the Office of the Surgeon General of the War Department had executed a complete study on losses of nutrients in the 100 canned items represented in the B ration as part of a large nutritional experiment at Camp Lee, Virginia. Army mess procedures were compared with "ideal" and "extreme" methods of preparation. In the meantime, the Office of Experiment Stations announced its extensive plan for studying institutional cooking in fifteen of the land grant colleges feeding Army and Navy personnel.

Results so far available from all of these studies have been assembled in "Tables of Food Composition Giving Proximate Mineral and Vitamin Components of Foods," released March 1, 1944. Over 250 foods are listed, approximately 40 being U. S. Army ration components. Since this table does not indicate the losses in cooking of foods, a supplementary table on "Vitamin Losses in Cooking Foods" has been prepared. Future revisions of these tables are contemplated as further data are obtained.

The Committee on Food Composition is to be commended for the speed and efficiency with which data essential for dietary evaluations are being made available.

NOTES

Nutrition in Small Industries

With the recognized necessity of highly nutritious food to ensure maximum efficiency and the need for feeding large numbers of people in a limited time, the war has brought to industrial management the problem of providing at least a portion of an adequate diet for their employees. The large industrial units have frequently met this responsibility by letting the service out on contracts to industrial caterers whose experience has included the application of sound restaurant practice to industrial needs. Since the larger catering companies often restrict their operations to plants employing a minimum of 800 to 2000 persons per shift, their experience is usually not available to the management of small plants who find the push for production, with its shorter lunch periods and additional shifts, outstripping the community facilities for providing adequate service.

Underwood, Stansel, and Ritter (*Indust. Med.* **13,** *160 (1944)*) of the Division of Industrial Hygiene of the Mississippi State Board of Health, utilize the lessons learned from group feeding in the large plants in outlining principles for the development of nutritional programs in small industrial units. The authors are concerned primarily with how, rather than what, to feed, and emphasize that the basic consideration which determines the success or failure of any change in the established customs of a plant is its effect on production.

The first step recommended in a program of in-plant feeding is provision of a clean, cheerful place where employees may eat. Such a lunchroom can be utilized for other purposes such as group meetings and recreation. The next step is establishment of a canteen in the lunchroom which will supply milk, fruits, nuts, and sandwiches as well as soft drinks and candy, and which will supplement and eventually replace the worker's lunch box. With this as a start it has been found that a steadily growing percentage of the food is supplied from a source in which the nutritious quality and quantity of food served can be controlled. From the beginning the employment of a dietitian or home economist who has specialized in institutional feeding is recommended.

The authors feel that there is abundant information on what the workers should eat, and that the problem is how to get them to eat it. The plan they present is a practical answer to the management's problem of getting the workers fed efficiently without sacrificing the advantages to be gained by the application of the scientific developments in the field of nutrition.

Mineral Oil and Nutrition

A recent publication of the Department of Agriculture warns that the increased use of mineral oil since the war in salad dressings and also in such foods as salted nuts, potato chips, and doughnuts, may have serious nutritional consequences. Experimentally it has shown that mineral oil interferes with the absorption of vitamins A and D and also of calcium and phosphorus.

Mineral oil has come into wider use in food preparation recently because it has not been rationed, as many food fats and oils have been, and because it is plentiful, relatively cheap, and does not become rancid. It has practically no taste so cannot be detected in salad dressing. Mineral oil dressing is widely sold also for "reducing" diets.

Unfortunately, few people understand the possible harmful effects of the continued use of mineral oil. Mineral oil has a useful function when properly used but its continued use over long periods of time, particularly if taken with food, may lead to nutritional disorders.

In a warning to physicians against the indiscriminate use of mineral oil, the *Journal of the American Medical Association* recently

stated: "The ingestion of mineral oil is capable of interfering seriously with the absorption of carotene, the precursor of vitamin A, with vitamin A itself, and also with vitamin D, calcium phosphorus and vitamin K. The prolonged use of mineral oil may be associated with disturbances related to deficiencies of such vitamins."

Socio-Economic Level and Dental Caries

Valuable data are now beginning to appear as a result of the examination of selectees for induction into the armed forces. A recent communication dealing with dental caries is based on the examination of 60,000 selectees in Boston (Hyde, *New Engl. J. Med.* **230,** *506 (1944)*). In this study a careful record was made of the number of decayed, missing, and filled teeth. The socio-economic level of each community from which the selectees came was estimated on the basis of a "desirability rating" based on such factors as medical care, educational facilities, public works, undesirably crowded housing, and the welfare rate per capita.

The results were of special interest in regard to their bearing on the possible cause of dental caries. It was found that the number of decayed teeth was greatest in those persons whose socio-economic level was lowest. The number missing, on the other hand, was not correlated with the socio-economic level. The number of filled teeth, as might be expected, was greatest in those from the best communities. Particularly noteworthy was the fact that the sum total of decayed, missing, and filled teeth, referred to as "DMF," was highest in selectees in the highest socio-economic level.

This interesting observation would suggest that the amount of dental caries is actually greater in persons from the best communities than in selectees from the poorest ones. As Hyde points out, it would, of course, be dangerous to accept this conclusion without qualification. In the first place, filled teeth may include many caries-free fissures that were filled and that would not have become carious. In the second place, the communities of low socio-economic level contain a somewhat large proportion of foreign-born and of races which may have better teeth than the American average. A study of the groups examined according to nationality revealed that in the Irish communities three times as many persons were disqualified because of dental defects as in the Portuguese and Russian-Jewish communities. The number of decayed teeth was found highest among the Irish and Portuguese and lowest among the Chinese and Russian-Jewish. The DMF was highest among the English and Irish and lowest among the Chinese and Negroes. The total amount of caries seemed to be independent of dental care. The fact that more men from the poorer communities than from the better ones were rejected for insufficient teeth appeared to be more indicative of the lack of reparative care than the amount of dental decay that had been present.

These observations agree with those of Klein and Palmer (*Pub. Health Reports* **55,** *187 (1940)*) who concluded that the incidence of dental caries was the same at all socio-economic levels. The question arises whether the supposedly superior nutrition of the better socio-economic levels may be poorer nutrition from the dental point of view. One may ask also whether the more extensive personal dental hygiene practiced in the better communities may be injurious or whether even the work of dentists may be responsible for the increased DMF in men from better communities. It is safe to say at least that improved socio-economic level does not guarantee less dental caries.

THE NUTRITION FOUNDATION

The Nutrition Foundation was organized by food and related manufacturers to develop and support a comprehensive research and educational program in the science of nutrition. It functions chiefly through grants in support of research in university centers where there are strong graduate schools in the basic sciences. Nutritional problems of immediate importance in relation to the war emergency receive special consideration.

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